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10/674,581	09/29/2003	Yuuki Tsutsui	019941-001810US	5398

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EXAMINER

HISSONG, BRUCE D

ART UNIT PAPER NUMBER

1646

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/674,581	Applicant(s) TSUTSUI ET AL.	
	Examiner Bruce D. Hissong, Ph.D.	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 and 21-27 is/are pending in the application.
- 4a) Of the above claim(s) 21-27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Formal Matters

1. Applicants' response to the office action mailed on 5/2/2006, including arguments/remarks and amended claims, was received on 10/2/2006 and has been entered into the record.

2. Claims 1-19 and 21-27 are currently pending. Claims 21-27 are withdrawn as non-elected subject matter, and claims 1-19 are the subject of this office action.

3. The text of those sections of Title 35, U.S.C. not included in this action can be found cited in full, in the previous office action mailed on 5/2/2006.

Claim Objections

1. Objection to claims 7, 12, and 18, regarding various grammatical issues, as set forth on page 2 of the office action mailed on 5/2/2006, is withdrawn in response to Applicants' amendments to the claims.

2. Claims 8 and 14 remain objected to for failing to further limit the subject matter of a previous claim, as set forth on page 3 of the office action mailed on 5/2/2006. In the response received on 10/2/2006, the Applicants argue that claims 8 and 14 recite the source of interferon (IFN)- α with greater particularity. This argument has been fully considered and is not persuasive. Claims 8 and 14 recite IFN- α that is either natural IFN- α , or recombinant-IFN- α . The Examiner is unaware of any other possible types of IFN- α , and therefore claims 8 and 14 are drawn to the very same types of IFN- α previously recited in claim 7. In addition, claim 2, which also recites an IFN- α selected from natural and recombinant IFN- α , is objected to for the same reasons as claims 8 and 14. The Examiner suggests separating embodiments drawn to natural and recombinant IFN- α into separate claims.

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3. The Examiner suggests the syntax of claims 5, 6, 10, 12, and 17 can be improved by amending the phrase "with which" to read "wherein".

4. The Examiner suggests the syntax of claim 1 can be improved by amending the phrase "...and an interferon α and which induces both...." to "and an interferon α , wherein said composition induces both.....". Furthermore, the Examiner also suggests amending the claim to read ".....at the mucosal surface, wherein said vaccine antigen and adjuvant of said vaccine antigen are administered via mucosal administration, and said vaccine antigen and adjuvant are administered.....".

5. The Examiner suggests the syntax of claim 10 can be improved by amending the claim to read "wherein said vaccine antigen comprises a protein or peptide antigen, and mucosal administration.....".

6. The Examiner suggests the syntax of claim 13 can be improved by amending the claim to read ".....and mucosal adjuvant, wherein said combined product induces both vaccine-antigen specific.....". Furthermore, the Examiner also suggests amending the claim to read ".....as the active ingredient, and wherein said mucosal adjuvant is administered via mucosal administration at the same time....".

7. The Examiner suggests the syntax of claim 19 can be improved by amending the claim to read ".....at the mucosal surface, wherein said mucosal adjuvant comprises an interferon.....".

Claim Rejections - 35 USC § 112, first paragraph – enablement

Rejection of claims 1-19 under 35 USC § 112, first paragraph, regarding lack of enablement for a mucosal adjuvant comprised of any IFN- α other than the murine IFN- α of Examples 1 and 2, as set forth on pages 3-5 of the prior office action mailed on 5/2/2006, is withdrawn.

In the response received on 10/2/2006, the Applicants argue that other sources of IFN- α can be readily determined, identified and screened using methods that are well-known in the art

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or described in the specification. The Applicants further argue that 2 working examples, including methods of screening IFN- α subtypes for effectiveness in inducing/promoting an immune response, are provided in the specification, and that screening even large numbers of IFN- α subtypes would not require undue experimentation. Therefore, one of ordinary skill in the art, using known sources of IFN- α and screening methods taught by the instant specification, would be able to determine which other IFN- α subtypes could be used in the claimed mucosal adjuvant. These arguments have been found persuasive, and therefore the rejection is withdrawn.

Claim Rejections - 35 USC § 112, first paragraph – written description

Rejection of claims 1-19 under 35 USC § 112, first paragraph, regarding lack of written description for the genus of IFN- α polypeptides that can be used as a mucosal adjuvant, as set forth on page 5 of the prior office action mailed on 5/2/2006, is withdrawn.

In the response received on 10/2/2006, the Applicants argue there are several known IFN- α subtypes, and specifically point to the teachings of Pestka (cited in the office action of 5/2/2006) which disclose 14 human genes that comprise the IFN- α family, and that "minor variants consisting of one or two amino acid differences account for the multiple alleles." The Applicants also state "in all likelihood, one or two amino acid differences will not make a difference with respect to a vaccine composition." Thus, the Applicants argue that because there are several known IFN- α subtypes with minor sequence differences between these subtypes, the IFN- α family has been defined by shared structural and physical properties, and any of these known IFN- α subtypes can be used as a mucosal vaccine adjuvant.

These arguments have been fully considered and are found persuasive, and therefore the rejection is withdrawn.

Claim Rejections - 35 USC § 102

Rejection of claims 1-2, 4-8, 10-14, and 16-19 under 35 USC § 102(b) as being anticipated by Staats *et al*, as set forth on pages 5-6 of the office action mailed on 5/2/2006, is withdrawn in response to Applicants arguments that Staats teaches the use of IFN-*gamma* as a mucosal adjuvant, and not IFN- α . This argument has been fully considered and is found

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persuasive, because although the disclosure of Staats recites "IFN α " in several places, it appears that Staats as defined "IFN α " to mean "interferon-gamma". Because the Office has no way of knowing whether its definition is erroneous or inadvertent (i.e. Staats *et al* really meant IFN-*alpha* rather than IFN-gamma), or was actually intentional, the rejection is withdrawn.

Claim Rejections - 35 USC § 103

Rejections withdrawn

1. Rejection of claims 3, 9, and 15 under 35 USC § 103(a) as being unpatentable over Staats *et al*, as set forth on page 6 of the office action mailed on 5/2/2006, is withdrawn in response to Applicants arguments that Staats teaches the use of IFN-*gamma* as a mucosal adjuvant, rather than IFN- α , as set forth above.

New grounds of rejection

2. Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Staats *et al* (WO 00/20028 – cited in the previous office action mailed on 5/2/2006), in view of Takasu (*Kurume Med J*, 2001, Vol. 48, p. 171-174). The claims of the instant invention are drawn to a vaccine composition comprised of a vaccine antigen and an IFN- α , wherein the vaccine antigen can be a protein or peptide antigen, and the IFN- α can be natural or recombinant IFN- α , and present in an amount ranging from 0.5 – 5,000,000 IU. The claims are also drawn to the vaccine composition comprised of a vaccine antigen and IFN- α , wherein both the antigen and the IFN- α are administered mucosally, and by the same route of administration, and at the same or different times, and wherein said composition induces antigen-specific antibodies in both the blood and at mucosal surfaces.

Staats *et al* teaches a method of eliciting an immune response by administration of a vaccine antigen and an adjuvant (see abstract, and claim 1). Staats *et al* teaches that the vaccine antigen can be either protein or peptide antigens, including protein/peptide antigens from a number of pathogenic organisms (see p. 21, line 11 – p. 23, line 2). Staats *et al* also teaches that various cytokines can be used as adjuvants (see p. 14, line 19 – p. 15, line 2, and claims 5-6). Furthermore, Staats *et al* teaches mucosal administration of the vaccine-adjuvant combination (claim 17), and also teaches that the vaccine-adjuvant induces both systemic

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(claim 22) and mucosal (claim 25) immune responses. Finally, by teaching that the vaccine and adjuvant are included together as a composition, Staats *et al* teach that the vaccine antigen and the adjuvant are administered at the same time and by the same route of administration. However, Staats *et al* is silent regarding the use of IFN- α as the adjuvant for any antigen-adjuvant combination or composition.

Takasu teaches that IFN- α is a potent adjuvant for increasing the immune response to various vaccine antigens. Specifically, Takasu discloses that co-administration of IFN- α with influenza virus peptide increased the cytotoxic T lymphocyte (CTL) response to the influenza virus peptide compared to vaccination with the influenza virus peptide alone (see p. 172-174, Figures 1-3).

Therefore, one of ordinary skill in the art, at the time the instant invention was conceived, would have been motivated to combine the teachings of Staats *et al* with those of Takasu to create a vaccine composition, or combined product, comprised of a vaccine antigen and IFN- α as an adjuvant, and administer said composition or combined product via mucosal administration, and furthermore, administer both the vaccine antigen and IFN- α together. The motivation to do so comes from the teachings of Staats *et al* which show that mucosal and systemic immunity can be induced by mucosal administration of a composition comprised of a vaccine antigen and a cytokine adjuvant, and Takasu, which shows that IFN- α is an adjuvant that effectively increases the immune response to peptide vaccines. Thus, one of skill in the art would be motivated to use the IFN- α adjuvant taught by Takasu as the adjuvant in the composition taught by Staats *et al*, and by doing so, would have a reasonable expectation of success in practicing the instant invention in a manner that is commensurate in scope with the claims.

Furthermore, although Staats *et al* does not teach using 0.5 to 5,000,000 IU of IFN- α in the adjuvant, it is noted that Takasu teaches IFN- α is an effective adjuvant when administered at a dose of 10^6 U, which is within the claimed dose range of the instant application. However, even if Takasu did not teach administration of IFN- α at this dose, one of ordinary skill in the art, at the time the instant invention was made, would be motivated to optimize the amount of IFN- α in order to produce a vaccine composition commensurate in scope with the claims of the instant invention. Such optimization would be within the abilities of a person of ordinary skill in the art, and would require nothing more than routine experimentation, thus giving the skilled artisan a reasonable expectation of success. Furthermore, it is noted that the claimed dose range of IFN-

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α is an exceedingly large, 10,000,000-fold range, and it is highly likely that any effective dose of IFN- α would fall within this range.

In summary, because the combination of Staats *et al* and Takasu teaches or suggests each limitation of the claims of the instant invention, one of ordinary skill in the art would have both the motivation, and a reasonable expectation of success, in practicing the instant invention by combining the teachings of Staats *et al* with those of Takasu.

2. Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster *et al* (US 6,436,391) in view of Tovey (US 6,361,769). The subject matter of the claims of the instant invention is discussed *supra*. Foster *et al* teaches the use of IFN- α as a vaccine adjuvant to increase B lymphocyte proliferation, and thus increase the effectiveness of vaccines (column 1, lines 52-56), and specifically recites co-administration of a vaccine with IFN- α , or alternatively, a composition comprised of IFN- α and a vaccine (column 1, lines 61-65). Foster *et al* is silent regarding mucosal administration of an IFN- α vaccine-adjuvant composition, and is also silent regarding specific amounts or doses of IFN- α . Tovey teaches a method of stimulating host immunity by oromucosal administration of IFN- α (column 2, line 32 – column 3, line 28). Tovey discloses specific doses of IFN- α that can be oromucosally administered (column 3, line 15-20), and also teaches that IFN- α can be administered as an adjunct to other therapy (column 3, lines 21-22), and specifically mentions previous studies in which IFNs were orally administered to enhance the efficiency of vaccines (column 1, lines 61-66).

It would have been obvious to a person of ordinary skill in the art, at the time the instant invention was conceived, to combine the teachings of Foster *et al* with those of Tovey to create a composition comprised of a vaccine antigen and IFN- α , wherein said composition is administered mucosally to stimulate antibody production in the blood and at mucosal surfaces. The motivation to do so comes from Foster *et al*, which shows that IFN- α can function as an adjuvant to enhance B cell proliferation and stimulate immunity, and Tovey, which teaches that IFN- α can be effectively administered via the oromucosal route. Both Foster *et al* and Tovey specifically teach or suggest co-administration of IFN- α with a vaccine antigen. Thus, a person of ordinary skill in the art would know that the response to vaccines can be enhanced by an IFN- α adjuvant, and that this adjuvant, as well as vaccine antigens, can be administered oromucosally. Furthermore, both Foster *et al* and Tovey, by teaching or suggesting co-

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administration of IFN- α and a vaccine antigen, would provide the motivation to combine both the vaccine antigen and IFN- α into one composition or combined product, and to administer both the vaccine antigen and IFN- α at the same time, and by the same route (oromucosal). Although neither Foster *et al* nor Tovey specifically teaches secretion of antibodies in the blood or at mucosal surfaces, the fact that Foster *et al* teaches enhancement of immunity, and specifically enhancement of B cell proliferation, after IFN- α administration, suggests that the combined vaccine antigen-IFN- α adjuvant composition suggested by Foster *et al* and Tovey would inherently possess the ability to enhance antibody production.

Furthermore, although Foster *et al* does not teach using 0.5 to 5,000,000 IU of IFN- α as an adjuvant, it is noted that Tovey teaches oromucosal administration of IFN- α at various doses, including 1500 IU, to preferably from about 500 IU to 20×10^6 IU, and most preferably from 1×10^4 – 1×10^6 IU (column 3, lines 15-20), which overlaps with or is within the claimed dose range of the instant application. However, even if Tovey did not teach administration of IFN- α at this dose, one of ordinary skill in the art, at the time the instant invention was made, would be motivated to optimize the amount of IFN- α in order to produce a vaccine composition commensurate in scope with the claims of the instant invention. Such optimization would be within the abilities of a person of ordinary skill in the art, and would require nothing more than routine experimentation, thus giving the skilled artisan a reasonable expectation of success. Furthermore, it is noted that the claimed dose range of IFN- α is an exceedingly large, 10,000,000-fold range, and it is highly likely that any effective dose of IFN- α would fall within this range.

In summary, the combined teachings of Foster *et al* and Tovey specifically teach, or suggest, each limitation of the instant claims, and therefore a person of ordinary skill in the art, at the time the instant invention was conceived, would have both the motivation, and a reasonable expectation of success, in practicing the instant invention as currently claimed by following the combined teachings of Foster *et al* and Tovey.

Conclusion

No claim is allowable.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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BDH
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ROBERT S. LANDSMAN, PH.D.
PRIMARY EXAMINER